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Patent
Attorney's Docket No. 033136-119

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	Confirmation No.: 3667
Richard G. Miller *et al.*	)	Group Art Unit: 1644
Application No.: 09/541,033	)	Examiner: Jessica H. Roark
Filed: March 31, 2000	)	Appeal No. 1
For: METHOD FOR TREATING AUTOIMMUNE AND ALLOIMMUNE DISEASES	)	

BRIEF FOR APPELLANT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This appeal is from the decision of the Primary Examiner dated February 20, 2002 (Paper No. 16), finally rejecting claims 1-11, which are reproduced as an Appendix to this brief. A Notice of Appeal was filed for this application on August 20, 2002 and filed herewith is a Petition requesting a 1 month extension of time for filing this Appeal Brief which is being filed on or before its now current due date of November 20, 2002.

A check covering the [X] $160.00 (2402) [ ] $320.00 (1402) Government fee and two extra copies of this brief are being filed herewith.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800. This paper is submitted in triplicate.

I. Real Party in Interest

The present application is not currently assigned; however, in the event that there is allowable subject matter in the application, Appellants intend to assign the application to Vasogen Ireland Ltd., which is the real party of interest.

II. Related Appeals and Interferences

The Appellants' legal representative, or prospective assignee do not know of any other appeal or interferences which will affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 1-11 are pending in the instant application.

In an Office Action (paper no. 6), Claims 1-11 were subject to an election of species requirement wherein three separate elections were required. Specifically, Applicants were required to elect:

a specific autoimmune or alloimmune disease treated by the claimed methods;

a specific stressor used to stress the autologous blood used in the claimed methods; and

a specific therapeutic treatment used in combination with the autologous blood for treating the selected autoimmune or alloimmune disease.

In response to this Office Action, Appellants elected the following:

rheumatoid arthritis as the specific autoimmune or alloimmune disease treated by the claimed methods;

a combination of a temperature of above body temperature, electromagnetic emission and an oxidative environment as the stressor; and

TNF inhibitor p75 TNFR:Fc as the therapeutic treatment.

Claims 1-11 are believed to read on this set of elected species.

In the Office Action mailed May 4, 2001 (paper no. 9), Claims 1-11, as directed to this set of elected species, were rejected under 35 U.S.C. §103(a) over Bolton, U.S. Patent

No. 5,980,954, and Jacobs, et al., U.S. Patent No. 5,605,690. In addition, Claim 6 was rejected under 35 U.S.C. §112, second paragraph.

In the final Office Action, the rejection of Claims 1-11 under 35 U.S.C. §103(a) over Bolton, U.S. Patent No. 5,980,954, and Jacobs, et al., U.S. Patent No. 5,605,690 was repeated and made final. However, the rejection of Claim 6 under 35 U.S.C. §112, second paragraph, was withdrawn.

In view of the above, Claims 1-11, as directed to this set of elected species, stand finally rejected under 35 U.S.C. §103(a) over Bolton, U.S. Patent No. 5,980,954, and Jacobs, et al., U.S. Patent No. 5,605,690.

In view of the above, this appeal is taken specifically with this rejection of Claims 1-11, as directed to this set of elected species, under 35 U.S.C. §103(a).

IV. Status of Amendments

In their response filed on December 7, 2002 (paper no. 14), Appellants requested an amendment to Claim 6. This amendment was entered by the United States Patent and Trademark Office. No other amendments have been requested.

V. Summary of the Invention

The invention relates to methods for the medical treatments of mammalian patients suffering from an autoimmune and an alloimmune disease. More specifically, as noted at from page 4, lines 3-9 and 15, of the substitute specification,[1] the claimed methods recite treatment of a mammalian patient (line 15) suffering from an autoimmune or an alloimmune disease. One of the specific diseases mentioned for treatment is rheumatoid arthritis (page 4, lines 3-5).

At page 4, lines 7-17, of the substitute specification, it is recited that the treatment protocol involves combination therapy. One component of this combination therapy

[1] A substitute specification was filed with the response to the Office Action mailed May 4, 2001 (paper no. 9). Appellants believe that the page and line numbering for this substitute specification is the same as the originally filed specification.

involves administration to a mammalian subject suffering from an autoimmune or alloimmune disease of a drug treatment to bring about at least a partial remission of the disease and/or one or more of the symptoms associated with the disease. Use of TNF inhibitor p75 TNFR:Fc as the drug in the therapeutic treatment is recited at page 7, lines 7-13, of the substitute specification.

As noted at page 4, lines 14-17, of the substitute specification, the other component of this combination therapy, involves the administration of autologous mammalian blood which has been modified extracorporeally by exposure to at least one stressor selected from the group consisting of an oxidative environment, an electromagnetic emission and a temperature above or below body temperature. A sufficient amount of this modified blood is administered to effectively maintain remission of the disease. See, for example, the paragraph bridging pp. 5 and 6 of the substitute specification.

All of these elements are found in appealed Claim 1.

As to the specific autoimmune and alloimmune diseases recited in Claim 2, the specification discloses such diseases at, for example, p. 4, lines 5-7 and p. 6, lines 12-17, which refer to the diseases recited on p. 1, lines 14-19; p. 7, lines 1-3 and 7-9; p. 8, lines 14-17; and Examples 1, 2, and 3, beginning at p. 14, line 5; p. 15, line 9; and p. 16, line 20, respectively.

As to the specific recitation of rheumatoid arthritis accompanied by symptoms including joint tenderness and swelling in Claim 3, the specification provides support at, for example, p. 3, lines 8-11 and pp. 7-8, throughout.

As to the specific recitation of TNF inhibitors in Claim 4, the specification provides support at, for example, p. 2, line 19 - p. 3, line 11; p. 4, lines 12-14; p. 7, lines 7-20; p. 8, throughout; and Examples 1 and 3, beginning at p. 14, line 5 and p. 16, line 20, respectively.

As to the specific recitation of TNF inhibitors selected from the group consisting of recombinant TNF receptors and anti-TNF monoclonal antibodies in Claim 5, the specification provides support at, for example, p. 2, line 19 - p. 3, line 11; p. 7, line 7 - p. 8, line 10; and Examples 1 and 3, beginning at p. 14, line 5 and p. 16, line 20,

respectively.

Support for the recombinant TNF receptors, p55 TNFR:Fc, of Claim 6, and p75 TNFR:Fc, of Claims 6 and 7, is found, for example, at, p. 3, lines 5-11; p. 7, line 7 - p. 8, line 10; p. 9, lines 1-4; and Examples 1 and 3, beginning at p. 14, line 5 and p. 16, line 20, respectively.

Support for the exposure of mammalian blood to the electromagnetic emission and elevated temperatures of Claim 8, is found, for example, at p. 4, lines 15-18; p. 9, lines 17-20; pp. 10-13, throughout; and Example 2, beginning at p. 15, line 9.

Support for the exposure of mammalian blood to ultraviolet light, as recited in Claim 9, is found at, for example, p. 12, lines 7-17; p. 13, lines 7-18; and Example 2, beginning at p. 15, line 9.

The simultaneous administration of a therapeutic treatment along with modified blood is descibed, for example, at p. 8, lines 11-22.

The consecutive administration of a therapeutic treatment along with modified blood is described, for example, at p. 8, lines 11-22 and Example 3, beginning at p. 16, line 20.

VI. The Issues

The single issue on appeal is whether Claims 1-11 are obvious over Bolton (U.S. Patent No. 5,980,954) in view of Jacobs *et al.* (U.S. Patent No. 5,605,690) under 35 U.S.C. § 103(a).

VII. Grouping of Claims

As to the single issue on appeal, all claims (1-11) are grouped together.

VIII. Argument

Claims 1-11 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bolton (U.S. Patent No. 5,980,954) in view of Jacobs (U.S. Patent No. 5,605,690). Final Office Action dated February 20, 2002 (Paper No. 16) at ¶ 7. Specifically, the Final Office Action alleges that it would have been obvious for one skilled

in the art to combine the teachings of the Bolton patent, directed to the use of stressed autologous blood to treat rheumatoid arthritis, with the teachings of the Jacobs patent, drawn to the use of recombinant, polypeptide TNF antagonists to treat arthritis, to develop a combination therapy comprising these separate inventions for the treatment of arthritis. Appellants respectfully traverse the rejection.

The Bolton and Jacobs patents teach away from the claimed combination therapy

Bolton describes the use of a portion of extra-corporeally-stressed autologous blood to alleviate the symptoms of certain autoimmune diseases. According to the teachings of Bolton, subjecting a patient's own cells to external stresses is believed to increase the ratio of TH2 cells relative to TH1 cells, thereby increasing the levels of regulatory cytokines in the blood upon reintroduction of the treated cells to the patient.

The Jacobs patent describes recombinant poplypeptide TNF antagonists of mammalian (not necessarily human) origin.

There is, however, no suggestion in Bolton that the disclosed methods of treatment are compatible with methods of treatment such as those described by Jacobs. Bolton states repeatedly in the Specification that the source of the cells and soluble blood components for making the disclosed autovaccines must be the same individual who will be treated with the resulting autovaccine. See, *e.g.*, column 2, lines 60-64; column 3, lines 2-5; and column 6, line 65 - column 7, line 10. Specifically, Bolton teaches that

> [a] significant feature of the present invention is that the source of the blood from which the autovaccine is prepared for a specific patient suffering from an autoimmune disease is the patient himself or herself. The antigens forming the basis of the autovaccine find their origin in the patient's own blood. *No extraneous antigens are added; the effective antigens are present in the patient's blood*, and/or are released or modified by the process of preparing the autovaccine using the patient's own blood as the source material.

'954 patent at column 6, line 65 - column 7, line 6; italics added. Thus, not only does Bolton fail to contemplate a combination of the disclosed autovaccines with any other form

of therapy, Bolton specifically states that no extraneous (*i.e.*, heterologous) antigens are to be added to the autovaccine. In this matter, the Bolton Specification is unambiguous in teaching away from the combination of the instant invention.

As above, the Jacobs patent describes recombinant poplypeptide TNF antagonists of mammalian (not necessarily human) origin. Jacobs specifically contemplates the use of primate, human, murine, canine, feline, bovine, ovine, equine and porcine TNFR (column 4, p. 42-45) as well as mutated, chimeric, and covalently modified derivatives of TNFR (throughout columns 4-7). Accordingly, if the polypeptide agonists of Jacobs were combined with the autovaccine of Bolton, the Jacobs antagonists could represent allelic variants, polypeptides from different mammalian species, or novel mutated or chimeric polypeptides. These are clearly not autologous antigens. One skilled in the art would immediately recognize that combining these heterologous, recombinant polypeptides with the Bolton autovaccine would contradict the specific teaching of the Bolton patent with respect to the use of autologous blood products. In fact, based on the teachings of the two prior art references, these inventions would appear to be incompatible since the introduction of foreign proteins to the stressed autologous blood would, by definition, make the reintroduced blood heterologous with respect to the clinical subject. For these reasons alone, the Bolton reference cannot be combined with the Jacobs reference to form the basis of an obvious rejection.

However, Appellants further note that the only combination therapy actually contemplated in the Jacobs Specification is that of a TNF antagonist (*i.e.*, receptor agonist) with an interleukin-1 or -2 receptor agonist. See, *e.g.*, column 13, line 61 - column 14, line 2; column 17, lines 24-28; and column 18, lines 10-40. These combinations represent the combination of multiple receptor agonists which presumably reduce autoimmune response through the same general mechanism of sequestering pro-inflammatory cytokines. There is no suggestion or motivation in the Jacobs patent to combine the disclosed antagonist therapy with a second therapy that fundamentally alters the regulation of cytokine production, as would the introduction of stressed autologous blood. As a result, while the Jacobs patent may not explicitly teach away from the combination with the Bolton

patent, neither would it motivate one skilled in the art to combine the claimed TNF antagonists with stressed autologous blood. Accordingly, there is simply no teaching in either reference that would motivate the practitioner to make or use the combination therapy of the instant application and no indication that such a combination would be successful.

In supporting its contention that it would have been obvious to one skilled in the art to combine the teaching of the Jacobs and Bolton patents, the Final Office Action relies on *In re Kerkhoven*, 205 USPQ 1069, 1072 (CCPA 1980) (*stating,* "[i]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose."). However, *In re Kerkhoven*, the practitioner was merely required to mix together two conventional spray-dried detergents to produce a composition comprising both detergents. Thus the practitioner was required to combine two similar compositions, which were intended to be delivered in the same manner, for the same purpose.

In contrast, the instant obviousness rejection is based on combining two therapies for arthritis, which involve distinctly different immunological mechanisms to bring about a therapeutic effect, and wherein at least one of the references explicitly teaches away from the combination. The proposed combination of prior art that underlies the instant obviousness rejection is factually distinct on several levels from the simple combination of spray detergents at issue in *In re Kerkhoven*. Accordingly, *In re Kerkhoven* is not germane to the instant case.

To maintain an obvious rejection, the Patent Office must show that the prior art references provide motivation for the combination, and some indication that such combination would be successful. *In re Vaeck*, 947 F.2d 488; 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). The practitioner would draw neither conclusion from the teachings of the two cited prior art references. In fact, Bolton and Jacobs appear to be biologically incompatible.

It is also well established patent law that *prima facie* obviousness is rebuttable by a showing that the references teach away from the claimed invention, as Appellants have

demonstrated. *In re Geisler*, 43 USPQ2d 1362, 1365 (Fed Cir. 1997). For at least this reason, Appellants submit the obvious rejection is improper and should be set aside.

IX. Conclusion

Appellants submit that the obviousness rejection cannot be maintained in the instant application. There is no motivation to combine the references; there is no suggestion of success in combining the references; the Bolton reference, in particular, teaches away from the combination; and the ability to successfully combine the stressed blood therapy with foreign proteins represents an unexpected result based on the teachings of the prior art. For at least the above reasons, Appellants request the rejection under 35 U.S.C. § 103(a) be overturned.

Respectfully submitted,

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APPENDIX A

Claims on Appeal:

1. A method for treating a mammalian subject suffering from an autoimmune or an alloimmune disease, the method comprising:

   administering to said subject a therapeutic treatment which results in at least partial remission of one or more symptoms of the autoimmune or alloimmune disease; and

   administering to said subject autologous mammalian blood which has been modified extracorporeally by exposure to at least one stressor selected from the group consisting of an oxidative environment, an electromagnetic emission and a temperature above or below body temperature, said modified mammalian blood being administered to said subject in an amount sufficient to maintain the remission of said one or more symptoms of the autoimmune or alloimmune disease.

2. The method of claim 1, wherein said autoimmune or alloimmune disease is selected from the group consisting of rheumatoid arthritis, multiple sclerosis, systemic lupus erythromatosis (SLE), scleroderma, diabetes, inflammatory bowel disease, psoriasis, atherosclerosis, graft versus host disease and tissue transplant rejection.

3. The method of claim 2, wherein said autoimmune or alloimmune disease is rheumatoid arthritis and said symptoms include joint tenderness and swelling.

4. The method of claim 2, wherein said therapeutic treatment comprises administration to said subject of one or more biologic tumor necrosis factor (TNF) inhibitors.

5. The method of claim 4, wherein said biologic TNF inhibitors are selected from one or more members of the group consisting of recombinant TNF receptors and anti-TNF monoclonal antibodies.

6. The method of claim 5, wherein said recombinant TNF receptor is selected from the group consisting of recombinant human TNF receptor p55 Fc fusion protein (p55 TNFR:Fc) and recombinant human TNF receptor p75 Fc fusion protein (p75 TNFR:Fc).

7. The method of claim 6, wherein said recombinant TNF receptor is p75 TNFR:Fc.

8. The method of claim 1, wherein said mammalian blood is modified extracorporeally by exposure to an electromagnetic emission, an elevated temperature and an oxidative environment.

9. The method of claim 8, wherein said electromagnetic emission comprises ultraviolet light.

10. The method of claim 1, wherein said therapeutic treatment and said modified mammalian blood are administered simultaneously.

11. The method of claim 1, wherein said therapeutic treatment and said modified mammalian blood administered consecutively.